Summary

Penicillin has a bactericidal action.

This action proceeds at a constant rate regardless of concentration within wide limits if pure penicillin is used: impure samples are more effective in low than in high concentrations.

This action is accelerated by increase in temperature throughout the range 4° to 42° C.

The action of penicillin is progressively impaired by an increase in the acidity of the medium between *p*H 7.0 and 5.0.

The behaviour of penicillin in diluted broth and in the presence of bacteriostatic agents supports the hypothesis that it acts only on dividing cells; the effect of temperature and the almost uniform susceptibility of cells from both old and very young cultures are against it.

I am indebted to the Penicillin Clinical Trials Committee of the Medical Research Council for most of the penicillin used, and to I.C.I. (Pharmaceuticals) Ltd. for the gift of 183 mg. of nearly pure penicillin. This work could not have been done without the assiduous technical assistance which was given by Miss P. M. Waterworth. For her services and for the equipment of the laboratory in which the work was done I am indebted to a fund, under the control of Mr. Rainsford Mowlem, which was generously provided by the United States organization "Bundles for Britain."

REFERENCES

Abraham, E. P., Gardner, A. D., Chain, E., Heatley, N. G., Fletcher, G. M., Jennings, M. A., and Florey, H. W. (1941). *Lancet*, **2**, 177.
Bigger, J. W. (1944a). Ibid., **2**, 142.
—— (1944b). Ibid., **2**, 497.
Hobby, Gladys L., and Dawson, M. H. (1944). *Proc. Soc. exp. Biol.*, N.Y., **56**, 178.
—— Meyer, K., and Chaffee, Eleanor (1942). Ibid., **50**, 281.
Miller, C. P., and Foster, Alice Z. (1944). Ibid., **56**, 205.
Rammelkamp, C. H., and Keefer, C. S. (1943). *J. clin. Invest.*, **22**, 649.
Rantz, L. A., and Kirby, W. M. M. (1944). *J. Immunol.*, **48**, 335.
Ungar, J. (1944). *Nature*, **154**, 236.
Withell, E. R. (1942). *J. Hyg.*, Camb., **42**, 339.

PENICILLIN IN GONORRHOEA AND SYPHILIS

WITH NOTES ON TWO CASES OF DUAL INFECTION

BY

F. L. LYDON, M.B., B.Ch.

Major, R.A.M.C.; Specialist in Venereology

AND

W. R. SCOTT COWE, M.B., Ch.B.

Capt., R.A.M.C.; Graded Venereologist

Middle East Forces

In recent years the widespread use of the sulphonamide group of drugs in the treatment of venereal diseases has had fairly satisfactory results. These drugs have been employed successfully in the treatment of gonorrhoea, soft sore, and other types of non-specific genital ulceration, and lymphogranuloma inguinale. However, from the clinical point of view certain difficulties were early encountered. These were due to the simple fact that a patient presenting the appearances of one venereal disease may well be incubating one or more of the others. Sulphanilamide itself, while almost uniformly successful in clearing an uncomplicated Ducrey infection, is not nearly so effective in the treatment of gonorrhoea. In fact, many cases of the latter infection treated with sulphanilamide developed afterwards a persistent mucoid or muco-purulent discharge due to such complications as anterior folliculitis or a posterior spread. Later a similar effect was seen in certain cases treated with inadequate or "self-administered" doses of sulphapyridine. These cases were extremely difficult to clear up and required prolonged hospital treatment.

The incubation periods of chancroid and gonorrhoea are roughly the same, and in addition a patient may have had more than one recent exposure to infection. Thus a man admitted to hospital a few days after his last exposure to infection and presenting a clinical chancroid might at the same time be incubating gonorrhoea. It became obvious, then, that in such a case the administration of sulphanilamide, while clearing the Ducrey infection, would in all probability mask the signs of the incubating gonorrhoea. In the early days this not infrequently happened. The patient was discharged from hospital with a healed sore and returned in a week or ten days with a persistent urethral discharge showing many pus cells, some secondary organisms, but no gonococci. There was no history of further exposure to infection. This type of case was peculiarly resistant to treatment, and generally one or other of the commoner complications of gonorrhoea was found. This difficulty was obviated by a routine which forbade the use of sulphanilamide in "sore cases" until at least 14 days after the last admitted exposure to infection.

These facts, when realized, are in the main a matter of clinical interest and do not present any serious problem or administrative difficulty. They serve, however, as an introduction to the theme of this short article, which is intended to point out the similar but much more serious difficulties at present attendant on the treatment of sulphapyridine-resistant gonorrhoea with penicillin.

Penicillin is now coming into general use in the treatment of resistant gonorrhoea cases, in which it has been found almost uniformly successful. In the first place, then, it will not be remiss to discuss what we know of its effect on the spirochaete of syphilis, more particularly as many—one might even say most—of the gonorrhoea cases so far treated have been within the incubation period of syphilis—that is, less than three months after the last exposure to infection.

The first observation to be made is on the report from the U.S.A. on 50 cases of early syphilis treated with penicillin, the dose used being 2,500,000 units. The details are not available here. So far as can be gathered, however, *Treponema pallidum* disappeared early from primary lesions, which healed rapidly, and the blood has remained Wassermann-negative for the present period of observation; while in early sero-positive cases there was a gradual reversal of the blood Wassermann to negative. This is as far as the story goes. It is a hopeful report, but we have no means of assessing what will be the ultimate outcome of these cases—i.e., whether this dosage is curative. In this connexion it would be well to remember that penicillin administered intramuscularly or intravenously does not pass into the spinal fluid unless perhaps in minute quantity. Therefore, since invasion of the central nervous system by *T. pallidum* is common in early syphilis, one consideration of vital importance is the possibility that C.N.S. involvement may show an increased incidence.

The second observation is on two cases of sulpha-resistant gonorrhoea recently under our care.

Case I

Pte. X. entered hospital on Sept. 11, 1944. Definite dates of exposure to infection were difficult to obtain accurately (language difficulty). Though he said that the last exposure was approximately seven weeks before admission, the clinical findings suggested a more recent one.

On examination the patient was found to have a purulent urethral discharge and a clinical syphilitic chancre in the coronal sulcus. He stated that the sore had been present for four weeks and the urethral discharge for a shorter period. A urethral smear showed many intracellular gonococci, and the urine was hazy in both glasses. Dark-ground examination showed the sore to be positive to *T. pallidum*. Routine sulphapyridine—27 g. over 5 days—was given, and anti-syphilitic treatment was withheld until the course was completed. A blood Kahn test on Sept. 12 was negative. On Sept. 19 a urethral smear still showed intracellular gonococci, and there was a muco-purulent urethral discharge with hazy urine in both glasses. On dark-ground examination the sore was again positive to *T. pallidum*. It was therefore decided to start penicillin treatment for the gonorrhoea and use the opportunity offered to observe the action of this drug on the primary syphilitic lesion.

On Sept. 19, 100,000 units of penicillin were administered intramuscularly in doses of 20,000 units three-hourly. Dark-ground examination of the sore was carried out before each injection of penicillin. The following observations were made: (1) The sore was positive to *T. pallidum* before the first, second, and third injections of penicillin but was negative thereafter—that is, after 60,000 units. (2) A mild general reaction was noted and the temperature rose to 100° F. six hours after the first injection. This reaction corresponded in time to the usual Herxheimer reaction found after initial arsenic in a primary case. Twenty other patients treated with the same batch of penicillin had no reaction. (3) The next day—Sept. 20—the sore was still negative to *T. pallidum* and considerably cleaner. Urethral discharge had ceased, and urine was clear in both glasses. (4) Daily examination showed the sore to be negative to *T. pallidum* on each succeeding day until Oct. 3—i.e., 14 days after starting penicillin treatment, and at this time had almost completely healed. (Only saline dressings had been applied.) (5) The following Wassermann and Kahn results were obtained at two different laboratories:—Lab. A: Kahn test negative on Sept. 21, 24, 29, and

Oct. 5. Lab. B: W.R. double positive, Kahn positive on Sept. 26 (W.R. + + ; K.T. +); W.R. and Kahn both negative on Oct. 5.

At this stage it was considered unjustifiable to withhold routine treatment with arsenic and bismuth. This was started on Oct. 5, and it was interesting to note that after the first 0.3 g. of N.A.B. there was mild general malaise and the temperature rose to 99° F. Further treatment has been uneventful. Kahn tests on Oct. 9 and 18 were both negative.

Comment.—Although the date of exposure to infection is not absolutely definite the expectation in this case would be that blood W.R. and Kahn tests would have been positive before routine treatment was instituted. A weak positive was obtained in one laboratory, but repeated controls at this and the other laboratory were all negative. Depending on the sensitivity of the antigen, this probably indicates that the penicillin had prevented an impending positive serum reaction.

Case II

Gnr. Y. was admitted to hospital on Aug. 28, 1944, with the following history: exposure to infection two weeks and three months previously; treated for fresh gonorrhoea with 27 g. of sulphapyridine in M.I. room from Aug. 21 to 28: urethral discharge persisted.

On admission he had a purulent urethral discharge with some oedema and induration in the region of the fraenum. Clinically this latter condition was suggestive of an intra-urethral chancre. A blood Kahn test on Aug. 28 was negative. A further course of sulphapyridine was given from Sept. 2 to 6. A urethral smear on Sept. 11 and succeeding days still showed intracellular gonococci, and the urine was hazy in both glasses. Perifraenal oedema and induration persisted, but over the period Sept. 2 to 14 nine dark-ground examinations of the urethral discharge were negative to *T. pallidum* despite the clinical appearances.

In view of the sulphapyridine-resistant gonorrhoea 100,000 units of penicillin were given on Sept. 18. A urethral smear on Sept. 20 showed no gonococci, but a slight watery discharge persisted until Oct. 2. Daily dark-ground examination of this was negative to *T. pallidum*.

He was discharged from hospital on Oct. 5. There was no urethral discharge, and the urine was clear in both glasses. The oedema and induration around the fraenal region had slowly subsided after penicillin therapy and had disappeared by the time the patient left the hospital.

Comment.—Although oedema as described above is occasionally present in acute gonorrhoea it usually does not persist so long even in sulpha-resistant cases. It is felt, then, that in all probability this was a case of intra-urethral chancre despite negative dark-ground findings. In view of this and the findings in Case I it is intended to prolong the period of post-hospital surveillance in this case, regular blood tests being carried out over a period of two years.

Discussion

The present dosage of penicillin used in the treatment of resistant gonorrhoea is 100,000 units, and a group of cases was recently reported in which 60,000 units were found adequate. These dosages, then, according to the presumptive evidence of reports on the treatment of syphilis, are quite inadequate to cure this disease, but on our own observations are perfectly adequate to effect the clinical cure of a primary lesion in itself. Obviously they will also very successfully mask any primary lesion which a patient with gonorrhoea may be incubating.

The following problems now arise: (1) What interval must elapse before such an inadequately treated case will develop a positive blood W.R. or systemic manifestations of syphilis? (2) On the analogy that an early syphilis inadequately treated with the arsenicals frequently develops precocious tertiary lesions, will this also hold true of penicillin? (3) On the same analogy, is not such a patient likely to remain infective during the assumed latent period? At present we have no evidence on these points.

What, then, is to be the routine in cases of sulpha-resistant gonorrhoea treated with penicillin? We know that a certain small but definite percentage of gonorrhoea cases are incubating syphilis, which may not show until the final blood test after three months' surveillance. The reasonable assumption now is that with the advent of penicillin these cases will be completely masked, according to the observations on the two cases quoted. Two alternatives appear to be open. Either the initial dosage must be sufficient to deal with a possible coexisting syphilis (2,500,000 units) or surveillance must be extended to cover a period of (say) two years after treatment to exclude the latent systemic spread of any possible coexisting syphilis to which the patient is exposed on the present routine. In our present state of knowledge the first is obviously wasteful. The second appears to be the only fair method, not only to the patient himself but also to the community in general.

Having reviewed briefly the probable effect of penicillin in masking an early syphilis it would be well at this stage to think of the numerous patients who have had penicillin treatment for general infections. Large numbers of these have been battle casualties with heavily infected wounds. With our knowledge of conditions in the various theatres of war it is reasonable to assume that any one of these cases may have been incubating syphilis at the time penicillin treatment was instituted, and the dose, though large, may not have been the postulated curative dose. Will the patient's signs and symptoms too be masked until in a few years' time the poor unfortunate begins at an early age to suffer from anginal pain or his wife gives birth to a snuffling child?

This article is not intended to be destructive or pessimistic, however much it may appear so. Penicillin has more than proved its value as a life-saving measure and in many acute and chronic infections which previously would have led to marked general debility and prolonged hospitalization. To the venereologist it is the drug of choice in the treatment of gonorrhoea. There is no doubt that as further supplies become available it will, and must, be even more extensively used.

However, it is hoped that enough has been said here to emphasize the need for the most careful and prolonged surveillance of penicillin-treated gonorrhoea cases (and even in cases where venereal disease might be suspected in a patient treated for some other condition) until our present knowledge of the effect of the drug in syphilis is much further advanced.

Regarding the second group of cases mentioned, it cannot be too strongly advocated that, in future, routine blood tests of the whole population should be enforced by law, particularly before marriage.

Conclusion

By force of circumstances this article has been largely theoretical and referable to a very small percentage of cases. However, until we know in detail the response of early syphilis to small doses of penicillin both from the clinical point of view and from that of change in the serum reaction, the necessity for very careful assessment and prolonged surveillance of every case would appear obvious, particularly in view of the two cases described.

THE TEMPORARY CHARACTER OF "FASTNESS" OF STAPHYLOCOCCI TO PENICILLIN

BY

E. W. TODD, M.D., D.P.H.

G. S. TURNER, A.I.M.L.T.

AND

L. G. W. DREW

(From the Inoculation Department, St. Mary's Hospital, and the Serum Institute, Wellcome Foundation, Carshalton, Surrey)*

It is generally assumed that micro-organisms which have been made resistant to bacteriostatic drugs or to antibiotic agents by continued subcultivation in increasing quantities of the antibacterial substance will remain "fast" after many subcultures in ordinary laboratory media. Fleming and Allison (1927) showed that *Micrococcus lysodeikticus* could be made resistant to lysozyme, and that after repeated subcultures extending over nine months in ordinary culture media this resistance was fully maintained. Similarly, bacterial resistance to sulphonamide drugs appears to be a permanent characteristic. McLeod and Daddi (1939) found that a "sulphapyridine-fast" strain of pneumococcus Type I remained resistant after 30 subcultures in broth.

Rake *et al.* (1944) subcultured pneumococcus Type III in penicillin 55 times, thereby raising the bacteriostatic dose of penicillin from 0.03 unit to 0.95 unit. After 32 subcultures of their resistant strain in ordinary blood broth the bacterio-

* Seconded for the duration of the war from the London County Council.